REMARKS

Claims 1, 12, 21, 22, 30, 31-36, and 38 have been amended herein. Claims 1-38 remain in the application. Favorable reconsideration is respectfully requested.

Claims 12, 21, 30, 34, 36, and 38 have been amended to be independent claims that incorporate all of the elements of the corresponding base claims and any intervening claims.

Claims 1 and 22 have been amended to remove the word "artificial" as applied to "transcription factors."

Claims 32 and 33 have been amended to correct a discrepancy in these two claims as filed.

Claims 31 and 35 have been amended to clarify that the anchor moiety is bonded to the nucleic acid target at a point proximate to the binding site, but not within the binding site. This clarification to Claims 31 and 35 is supported by, for example, Claims 1 and 13 as originally filed.

No new matter added.

With respect to Claim 36, Applicant notes that this claim was not subject to any rejections in the Office Action dated September 20, 2006 (but did depend from a rejected base claim). Claim 36 has been re-written herein as an independent claim. Applicant therefore submits that Claim 36 is now in condition for allowance.

Rejection of Claims 1-12 and 22-30 Under §112, Second Paragraph:

This rejection is believed to have been overcome, in part, by appropriate amendment to the claims, and is, in part, respectfully traversed.

With respect to the phrase "artificial regulatory factors," this portion of the rejection is believed to have been overcome by amending Claim 1 to remove the qualifying phrase "natural or artificial," and by amending Claim 22 to remove the qualifying phrase "artificial." Applicant thus submits that this portion of the rejection has been rendered moot.

With respect to the phrase "entropically destabilized" as used in Claims 12, 21, 30, 34, and 38, Applicant respectfully traverses this portion of the rejection because the phrase "entropically destabilized" is both explicitly defined in the specification and is readily understood by one of skill in the art. Entropy, of course, is a thermodynamic value. It is one of the factors that determines the free energy of a system. As used in the present claims, the phrase "entropically destabilized" is explicitly linked to a positively recited outcome, namely that the linker moiety confers conditional

behavior upon the isolated nucleic acid target. The linker behaves in one fashion at a first temperature, and behaves in a second, distinct fashion at a second temperature different than the first. As a general proposition, "entropically destabilized," simply means that the linker is flexible. In particular, see the application as filed at page 25, lines 18-28:

> Not surprisingly, increasing linker length inflicts an energetic penalty on the ability of the test compound to recruit the regulatory factor to an adjacent nucleic acid binding site. However, this penalty can be tuned such that a bifunctional molecule capable of functioning at lower temperatures is rendered incapable of binding under physiological temperatures. Thus, rather than minimizing linker entropy when creating multivalent ligands (as in the prior art), by destabilizing the linker (via increased entropy) the linker creates a conditional "chemical switch." Temperature sensitivity thus permits rapid spatio-temporal control of the activity of the test compound bonded to the linker. The utility of this approach is that the flexible linker will behave differently at different temperatures, due to the increased entropy inherent in a longer linker. This characteristic of entropically destabilized linkers is designated herein as "conditional behavior."

Applicant thus submits that the term "entropically destabilized" is sufficiently well described in the specification such that a person of ordinary skill in the art knows whether a linker meets the limitation of being "entropically destabilized." As noted in the above passage, to be considered "entropically destabilized," the linker must function as a "chemical switch."

In light of the amendment to the claims and the above remarks, Applicant submits that the rejection of Claims 1-12 and 22-30 under §112, second paragraph has been overcome. Withdrawal of the rejection is respectfully traversed.

Rejection of Claims 1-10, 13-19, and 31-32 Under §102(b) in View of Ansari et al. (2001) *Chem. Biol.*, 8:583-592, Published Online on May 8, 2001:

This rejection is respectfully traversed because the claims are not drawn to an artificial transcription activator as described in the Ansari et al. paper. Rather, Claims 1-10 and 13-19 are drawn to methods for evaluating whether a test compound modulates binding of a regulatory factor to its corresponding binding site on a nucleic acid (Claims 1-10) and for evaluating whether a test compound can facilitate, recruit, or stabilize binding of a natural regulatory factor to its corresponding binding site (Claims 13-19). Claims 31 and 32 are directed to compositions of

matter comprising (in the case of Claim 31) a nucleic acid target that defines a binding site for a regulatory factor, and anchor moiety covalently bonded to the nucleic acid target (at a point outside the binding site), a linker moiety bonded to the anchor moiety, and a test compound conjugated to the linker moiety.

For a clear understanding of the claimed invention, it is critical to definee the various chemical entities that are involved in transcription and how the process of transcription proceeds. Exhibit A, attached hereto, schematically depicts the process of transcription as it is presently understood. Briefly, a transcription factor, comprising an activation domain ("AD," red square) and a sequence-specific DNA-binding domain ("DBD", blue oval) bind upstream of the gene to be transcribed. The binding site itself is a gene-specific regulatory sequence; that is, different genes have specific sets of DBDs which may vary from gene to gene. Once the transcription factor binds to the regulatory sequence (in a sequence-specific binding), the bound transcription factor is recognized by the transcriptional machinery and transcription begins. As noted in the Ansari et al. paper, the activation domain is the key functional module of the transcription factor. The activation domain of the transcription factor is thought to bind to "several components of the transcriptional machinery." The transcriptional machinery itself is a collection of comparatively large, multi-subunit complexes that are associated with the RNA polymerase II holoenzyme. ("RNA Pol II" in Exhibit A; see also Ansari et al., at page 583, right-hand column.)

It is important to note that the transcription machinery itself **is not** gene specific. The DNA-binding domain of the transcription factor **is** sequence specific. The transcription machinery functions to transcribe any gene to which it is recruited by a recognizable, gene-specific transcription factor. Thus, as shown in Exhibit A, a transcription factor comprising an activation domain and a DNA-binding domain binds with sequence-specificity (via the DBD) to the gene-specific regulatory sequence within the target DNA. The transcription machinery is the recruited to the gene by an interaction with the activation domain of the transcription factor and begins to transcribe the downstream gene sequence.

With that background, note that the Ansari et al. paper describes an artificial transcription factor. See section 1.2 of the Ansari et al. paper, starting at page 584, right-hand column. Thus, in the Ansari et al. paper, the authors constructed an artificial transcription factor that consisted of a polyamide DNA-binding domain (designed to bind to the sequence 5'-TGTTAT-3'), a flexible

tether, and one of three different activation domains based on VP16, a viral protein. A schematic diagram of this artificial transcription factor is shown in Fig. 1 of the Ansari et al. paper (at page 584) and in Exhibit B, attached hereto. As shown in Exhibit B, Ansari et al's artificial transcription factor very closely mimics a real transcription factor. Referring to Exhibit B, Ansari's artificial transcription factor consists of a DNA-binding domain ("DBD," blue triangle) linked to an activation domain ("AD," red hexagon), via a tether (black zig-zag line linking the DBD and the AD).

There are three critical distinctions between the artificial transcription factor taught by Ansari et al., and the method and composition of matter recited in the present claims:

First, the present claims do not recite an artificial transcription factor.

Second, the artificial transcription factor described in Ansari et al. includes a polyamide DNA-binding domain that binds **within** the actual DNA recognition domain for the natural transcription factor. See Ansari et al., section 2.5, at page 590. See also section 4.3 of the Ansari et al. paper (at page 591) which describes the construction of the DNA target used for the *in vitro* transcription experiment described in Ansari et al. The DNA target was fabricated with the appropriate palindromic recognition sequences for the polyamide DNA-binding domains of Ansari's artificial transcription factor. These palindromic recognition sequences were then purposefully placed in the proper orientation with respect to a downstream TATA box. Thus, Ansari's *in vitro* transcription assay used a target DNA wherein the artificial transcription factor was explicitly designed to bind within an actual binding site (and thus to initiate transcription via an interaction with the transcription machinery itself).

Third, the artificial transcription factor of Ansari et al. is explicitly designed to interact directly with "targets in the transcription machinery." See Ansari et al. at page 588, right-hand column, first full paragraph. To accomplish that goal, Ansari et al. used a longer tether (or incorporated an internal pyrrole residue into an otherwise short tether) to project the activation domain away from the DNA (so that the activation domain can more easily interact with the transcriptional machinery). See page 589 of Ansari. The present invention does not recite an activation domain at all. In other words, Ansari et al. **do not** describe a construct that interacts with a gene-specific transcription factor or a regulatory factor. Ansari et al. describe an artificial transcription factor itself.

This is distinctly different from the present invention. The present method does not use an artificial transcription factor, but employs a construct that interacts with a transcription factor (or other regulatory factor). Thus, the present claims positively require two elements that are not described in the Ansari et al. paper. First, the nucleic acid target of the present invention has bound to it an anchor moiety. However, **unlike the Ansari et al. paper**, the anchor moiety in the present invention is bonded to the nucleic acid at a point "**proximate to, but not within**" the binding site for a regulatory factor. This is a positive limitation of all of the present claims. (Note that claims 31 and 32, which are drawn to compositions of matter, positively require that the anchor moiety be covalently bonded to the nucleic acid target at a point proximate to the regulatory factor binding site, but not within the binding site.) In contrast, the artificial transcription factor of Ansari et al. **must** bind within the corresponding binding site on the DNA target to be transcribed.

Second, the present method uses a construct that interacts not with the transcription machinery (as in Ansari et al.), but with a regulatory factor (such as a transcription factor or other nucleic acid-binding molecules). See Exhibits C and D, attached hereto, which illustrate schematically the method of Claim 1. Rather than being an artificial transcription factor (as described in Ansari et al.), the present invention uses a construct that includes an anchor that binds **outside of** the binding site for a transcription factor (or other regulatory factor). The anchor moiety of the present claims is depicted as "DBD" in Exhibits C and D. The anchor is connected to a linker, shown as a dashed line in Exhibits C and D. Lastly, a test compound, shown as a hook in Exhibits C an D is attached to the linker. In the present invention, the test compound interacts with the DBD of a regulatory factor, such as a transcription factor.

This is utterly different than the artificial transcription factor described in Ansari et al. The present claims are not directed to artificial transcription factors, but to a method to evaluate test compounds for their ability to modulate the binding of regulatory factors (such as transcription factors) to their corresponding DNA binding sites. The composition recited in Claims 31 and 32 does not bind to the transcription binding site (as does the artificial transcription factor of Ansari et al.), but binds proximate to it, so that the test compound can access and interact with the transcription factors (or other regulatory factors) that are capable of binding within the binding site. In short, the binding site remains open for regulatory factors to bind to it. The present

method places a construct at a point proximate to the binding site (not within it) as a means to evaluate the test compound for its ability to interact with these regulatory factors.

For these reasons, Applicants submits that the rejection of Claims 1-10, 13-19, and 31-32 under §102(b) in view of Ansari et al. is untenable. Withdrawal of the rejection is respectfully requested.

Rejection of Claims 22-28 Under §102(b) in View of Ansari et al. (2001), with Additional Evidence Provided by Sadowski et al. (1998) *Nature*, 335:563-564:

This rejection is respectfully traversed because when read in combination, Ansari et al. and Sadowski et al. result in the artificial transcription factor described by Ansari et al, that uses the GAL4-VP16 activation domain described in Sadowski et al. The resulting construct is still an artificial transcription factor per se, rather than a construct that interacts with transcription factors.

The discussion above with respect to the Ansari et al. paper is incorporated herein in full. Briefly recapping, Ansari et al. describe an artificial transcription factor. In both Ansari et al. and Sadowski et al., the artificial transcription factor interacts directly with the transcriptional machinery. Ansari et al. state that the activation domain of their artificial transcription factor is designed to interact with "targets in the transcription machinery." See Ansari et al. at page 588, right-hand column, first full paragraph. Likewise, Sadowski uses GAL4-VP16 to "interact with some component of the transcriptional machinery." See the abstract of Sadowski et al.

It is especially critical to note that Sadowski et al. **do not** teach or suggest that the GAL4-VP16 is a transcription activator that can modulate binding of natural, **gene-specific** transcription factors (not general transcription factors), as alleged at the bottom of page 7 of the Office Action. (The Office provides no pin-point citation for this conclusion.) Applicant notes that the binding sites for the GAL4 portion of Sadowski's construct were purposefully engineered into the CHO cells. Those binding sites are not present in the native CHO cells. See page 563, right hand column, first full paragraph of Sadowski et al.: "Reporter plasmids are distinguished by the presence (or absence) of insertions in the yeast sequence UAS_o that contains four GAL4 binding sites." Thus, Sadowski engineered into their construct the binding sites on the DNA target, and then positioned the binding sites at various locations relative to the gene to be transcribed. In

effect, Sadowski simply engineered into their system a suitable binding site for their artificial transcription factor. But in every instance, the GAL4 portion of the GAL4-VP16 construct binds to that specific binding site (which was inserted solely so that the GAL4-VP16 fusion protein would have place to bind). Contrary to the assertion made by the Office, Sadowski et al. do not teach or suggest that their GAL4-VP16 "modulates" the binding of natural, gene-specific transcription factors to their corresponding natural binding sites. In fact, when the GAL4 binding site was omitted from the construct, no transcription resulted. See Sadowski et al. at page 566, left-hand column, first paragraph: "Activity was not detected in either cell line... when the UAS_G was positioned at -1180 or +1850, and in no case did GAL4 activate."

Sadowski et al. also do not describe any type of linker between the GAL4 and the VP16 portions of their construct. Thus, looking at Ansari et al. in light of Sadowski et al. yields an artificial transcription factor as described by Ansari et al, with the parts slightly rearranged. The combination yields an artificial transcription factor consisting of Ansari's polyamide DNA-binding domain (or the GAL4 binding domain of Sadowski et al.), the polyether tether as taught by Ansari et al. (Sadowski's construct has no tether), and the VP-16 activation domain as described by Sadowski et al. The result is still an artificial transcription factor. The present claims, however, are not directed to an artificial transcription factor.

As noted earlier, the present claims positively require two elements that are not described in the combined teachings of the Ansari et al. paper and the Sadowski et al. paper. First, the nucleic acid target of the present invention has bound to it an anchor moiety. Unlike the Ansari et al. and Sadowski et al., the anchor moiety in the present invention is bonded to the nucleic acid at a point "proximate to, but not within" the binding site for a regulatory factor. Clearly, this cannot be the case in Sadowski et al. because Sadowski et al. purposefully engineered into their plasmid up to four binding sites for the GAL4 portion of their fusion protein. Sadowski et al. go on to note that their construct interacts with components of the "transcriptional machinery," not the native transcription factors themselves. See the abstract of Sadowski et al.

Note also that Sadowski et al. themselves explicitly state the high activation activity of GAL4-VP16 is **unlikely** to be increased DNA binding. Sadowski et al. note that GAL4 efficiently fills GAL4 binding sites *in vivo*. See Sadowski et al. at page 564, left-hand column, second full paragraph:

> Why is GAL4-VP16 such a powerful activator? It is highly unlikely that the distinctive properties of the molecule can be ascribed to, for example, increased DNA binding. A variety of experiments suggest that GAL4 (1-147) forms stable dimers... and that this fragment, as well as other GAL4 derivatives, efficiently fill the GAL4 binding sites *in vivo*.

Thus, the artificial transcription factor of Ansari et al., even when modified to include either the GAL4 or the VP16 portions of Sadowski's construct **must** bind within the binding site for the corresponding natural transcription factor binding site. Sadowski explicitly states that GAL4 binds within its corresponding regulatory binding site *in vivo*. And the Ansari et al. paper is directed explicitly to an artificial transcription factor designed to bind within a specific transcription factor binding site.

Additionally, in both Ansari et al. and Sadowski et al., the construct interacts with the transcription machinery itself, rather than with a gene-specific regulatory factor, such as a transcription factor. The distinction is illustrated in Exhibit B, which shows schematically the Ansari et al.-Sadowski et al. combination, as compared to Exhibits C and D, which schematically illustrate the present invention.

The present invention is not an artificial transcription factor. The construct required by the present claims includes an anchor that binds **outside of the binding site for a transcription factor** (or other regulatory factor). The combination of Ansari et al. and Sadowski et al., in contrast, describes an artificial transcription factor that binds within the binding site for a natural transcription factor (GAL4- in the case of Sadowski et al.).

Applicant thus submits that the rejection of Claims 22-28 under §102(b) in view of Ansari et al., with additional evidence provided by Sadowski et al. is untenable. Withdrawal of the rejection is respectfully requested.

Rejection of Claims 1-4, 8-9, 11, 13, 17-18, 20, 31, 33, 35, and 37 Under §102(e) in View of Stanojevic, U.S. Patent Application Pub. No. 2003/105,045:

This rejection is respectfully traversed because the Stanojevic publication, like the Ansari et al. paper, is limited entirely to a description of artificial transcription factors. In short, DNA-binding domain as described in Stanojevic is purposefully designed to bind within the binding site for a transcription factor. In contrast, all of the present claims require that the recited construct

include an anchor moiety that binds at a point proximate to, but not within, the regulatory factor binding site.

More specifically, the Stanojevic publication is clearly directed to artificial transcription factors (ATF's). See paragraph 10 of Stanojevic. Here, Stanojevic notes that his ATF's are modular, and include a DNA-binding domain and an effector domain. Stanojevic's main goal, as articulated in paragraph 10, is to introduce new, drug-like properties into the ATF's, while still maintaining their ability to regulate RNA transcription of specific genes.

Of particular note is that, like the Ansari et al. paper discussed above, the ATF described by Stanojevic must bind within a promoter binding site in order to function as a transcription factor. In particular, see paragraph 41 of the Stanojevic publication:

> The choice of DNA binding domain depends on the gene intended to be activated. The DNA binding domain recognizes a site that is typically positioned relatively near to the transcriptional start site of the gene for which the activator can affect transcription, although some activators may be able to act over long distances. Many activators or repressors are able to act over long distances and use of these effectors is contemplated in the invention.

The point here is that Stanojevic's construction is an artificial transcription factor. The present claims are not directed to an artificial transcription factor.

See also paragraph 55 of Stanojevic, which discusses his artificial transcription factors in the context of ATF's that suppress transcription, rather than activate it:

> In at least some other embodiments of the invention, the effector is selected to repress transcription. Attachment of repressor domains, *i.e.*, synthesis of repressor ATFs, is contemplated. Natural transcriptional factors typically contain activation domains or repression domains, and in some cases they may contain both activation and repression domains [citations omitted]. Transcriptional factors containing repressor domains function in an analogous manner as transcriptional factors containing activator domains, that is, they both need to bring the respective domains in the vicinity of the promoter DNA to exert the effect on RNA transcription [citations omitted]. As opposed to transcriptional activators, **the binding of a transcriptional repressor to the promoter** results in the decrease in the levels of RNA transcription. **This effect is caused by the interference of transcriptional repressor domains with the assembly of the Polymerase II holoenzyme complex through a variety of different mechanisms.** These mechanisms range from rearrangements of a chromatin structure through histone deacetylation to interference with action of activation domains [citations omitted]. While the repressor domains are very diverse and share very few common structural features, for the most part their net effect on a target gene transcription

is similar. (Emphasis added.)

Stanojevic's ATF thus clearly functions in the same fashion as a natural transcription factor: they bind within the promoter recognition site, where they then interact with the transcriptional machinery itself.

This is totally different from the present claims, which positively require that the anchor bind at a point outside the binding site for the regulatory factor.

On this issue (the location of the binding of the Stanojevic's ATF), note that Stanojevic, like Sadowski, uses a test system that simply incorporates suitable binding sites at appropriate locations relative to the gene to be transcribed. See Figs. 3A and 3B of Stanojevic, and the accompanying description at paragraph 57 of Stanojevic:

> Transcriptional assays for repression *in vitro* and *in vivo* may be performed with templates that, for example, contain both ATF and GAL4 binding sites. The repressor ATFs are tested for their ability to inhibit the transcriptional activation mediated by GAL4-VP16 and other strong activation domains fused to the GAL4 DNA-binding domain. Alternatively, the assays for repression may be performed with transcriptional templates **that contain the ATF binding sites incorporated in the promoter** having a constitutively high level of basal transcription such as the CMV immediate early enhancer-promoter (Schmidt et al., Mol. Cell. Biol. 10: 4404-4411 (1990)). In this case, **the binding of the ATF repressor to the promoter** will result in the decrease in RNA transcription, and the presence of additional binding sites for transcriptional activation is unnecessary.

As is made clear from this passage, Stanojevic's ATF is purposefully designed to bind within the promoter region itself – that is, within binding site for a regulatory factor. In contrast, Claim 1, for example, explicitly requires that the nucleic acid target include an anchor moiety that is bonded at a point proximate to the regulatory factor binding site, but not within the binding site. Because Stanojevic's approach is to make an entire ATF (as illustrated in Exhibit B), Stanojevic's ATF is purposefully designed to bind within the binding sites utilized by natural transcription factors.

Lastly, see paragraph 96 of the Stanojevic publication, which addresses Stanojevic's view about why his ATFs could be more potent than the GAL4-VP16 construct:

> In fact, the *in vitro* transcription assays described in FIGS. 3 and 4 imply that the ATFs could be even more potent transcriptional activators than GAL4-VP16. For example, **GAL4-VP16 protein binds to each of the five sites in the promoter as a dimer, while ATF molecules bind the corresponding triple-helix target**

> **sites as monomers** [citations omitted]. However, five ATF molecules **bound to the promoter** elicit a similar effect on transcription *in vitro* compared to ten GAL4-VP16 molecules (FIG. 4). This high potency of ATF molecules may be due to the simple extended chemical structure involving no bulky protein domains that leaves effectors much more exposed **to interaction with RNA Polymerase II holoenzyme** and/or other proteins. The exposed effector would in effect **facilitate the recruitment of the holoenzyme to the promoter and the initiation of RNA transcription**.

As noted in this passage, Stanojevic's ATF is designed to bind within the promoter region itself, so that the effector portion of the construct can interact directly with the transcription machinery (*i.e.*, the RNA Pol II enzyme complex). The present claims, in contrast, use a construct purposefully designed to bind **outside** of the regulatory factor binding site. Thus, the last step of Claim 1 positively requires a determination of whether the binding of the regulatory factor to its binding site defined in the nucleic acid target is modulated by presence of the test compound. Stanojevic's approach does not include any such step because Stanojevic is not looking at modulating the binding of a regulatory factor (such as a gene-specific transcription factor) to its binding site on the DNA target. Rather, Stanojevic describes an entire artificial transcription factor per se. Stanojevic's ATF binds within the promoter region and either up-regulates or down-regulates transcription based on the nature of the effector domain included in the ATF. The present claims, however, **are not** directed to ATF's, but rather to constructs that modulate the binding of regulatory factors (such as gene-specific transcription factors) to their cognate binding sites on a DNA target.

Applicant therefore submits that the rejection of Claims 1-4, 8-9, 11, 13, 17-18, 20, 31, 33, 35, and 37 under §102(e) in view of Stanojevic is untenable. Withdrawal of the rejection is respectfully requested.

Rejection of Claims 1, 3-4, 8-10, 13, 15, 17-19, 22, 26-28, and 31-32 Under §102(a) in View of Stanojevic & Young (2002) *Biochem.*, 41:7209-7216:

This rejection is respectfully traversed on essentially the same grounds articulated in the prior section of this response. The Stanojevic & Young paper is limited to a description of artificial transcription factors (ATF's). The present claims, however, are not directed to ATF's, but to constructs that modulate the binding of a regulatory factor (such as a transcription factor)

to its corresponding binding site on a DNA target. The present claims positively require that the anchor moiety bind at a point proximate to a regulatory factor binding site, but not within that binding site.

In contrast, the Stanojevic & Young paper describes an ATF that binds **within** a corresponding promoter region (*i.e.*, within a corresponding regulatory factor binding region) in the target DNA. In particular see the passage at page 7210, right-hand column, last paragraph of the Stanojevic & Young paper and Figs. 3A and 3B of Stanojevic & Young paper. The passage at page 7210 explicitly states:

> As a DNA-binding domain, we utilized the 22-mer triplex-helix-forming oligonucleotide (TFO). The TFO's have been used to target specific DNA sequence and **sites in gene promoters** for over a decade [citations omitted].

Figs. 3A and 3B of the Stanojevic & Young paper are schematic diagrams of the control transcription template and the ATF transcription template, respectively. The control template contains five GAL4 binding sites **incorporated into the promoter region**. The ATF transcription template contains five ATF binding sites instead of the GAL4 binding sites. In short, Stanojevic & Young created a transcription model that included a binding site for the ATF engineered directly into the target DNA at an appropriate position relative to the TATA box shown in the figures. Stanojevic & Young's ATF bound within that regulatory factor binding site. The sites were purposefully created by Stanojevic & Young so that their ATF would have a place to bind. In short, Stanojevic & Young created both an ATF, and a corresponding binding site for the ATF. If the corresponding binding site for Stanojevic & Young's ATF is omitted, the construct fails to function. See page 7212, right-hand column, bottom of Stanojevic & Young: "This effect [the binding of the ATF to the promoter region] is sequence specific since none of the ATFs were able to activate transcription from the control template lacking the ATF binding sites."

In contrast, however, the present claims positively require that the construct bind proximate to, but not within, the regulatory factor binding site. This positive limitation of the claims is neither described, nor suggested by the Stanojevic & Young paper. Stanojevic & Young explicitly teach providing the regulatory factor binding site itself, as well as an ATF that binds in a sequence-specific fashion to the regulatory factor binding site.

Applicant therefore submits that the rejection of Claims 1, 3-4, 8-10, 13, 15, 17-19, 22,

26-28, and 31-32 under §102(a) in View of Stanojevic & Young is untenable. Withdrawal of the rejection is respectfully traversed.

Rejection of Claims 1, 11, 13, 20, 31, and 33 Under §103(a) over Ansari et al. (2001) in View of Arora et al. (2002) *J. Am. Chem. Soc.*, 124:13067-13071:

This rejection is respectfully traversed because the combination of Ansari et al. and Arora et al. results in an artificial transcription factor (ATF) of the type described by Ansari et al, using the poly-L-proline linker described in Arora et al. The outcome is simply another type of ATF that is specifically designed to bind **within** the regulatory factor binding site in the target DNA and then to interact, via an activation domain, with the transcription machinery itself. In particular, see Figure 1 of the Arora et al. paper, which is a schematic diagram of Arora's artificial transcription factor. Note that Fig. 1 of Arora et al. is substantially identical to Exhibit B submitted herewith and discussed earlier. The combination of Ansari et al. with Arora et al. thus yields an ATF having the DNA-binding domain and affector domains as described in Ansari et al., coupled with the poly-L-proline linker described in Arora et al.

In both Ansari et al. and Arora et al., the DNA-binding domain of the ATF is purposefully designed to bind **within** the corresponding regulatory factor binding site present on the DNA target. This is best shown in Fig. 1 of Arora et al. The ATF described by the combination of Ansari et al. with Arora et al. does not interact with other transcription factors, but initiates transcription by a direct interaction of the activation domain of the ATF with the transcription machinery.

Thus, as noted above with respect to Ansari et al. taken alone, there are two critical distinctions between the artificial transcription factor taught by the combination of Ansari et al. and Arora et al., and the method and composition of matter recited in the present claims. The combination of these two references yields an ATF essentially identical to Ansari's ATF, but with Arora's poly-L-proline linker. Thus, Arora et al. is largely cumulative to the teaching of Ansari et al. First, the ATFs described in Ansari et al. and Arora et al. include a polyamide DNA-binding domain that binds **within** the actual DNA recognition domain for the natural transcription factor. See Ansari et al., section 2.5, at page 590. See also section 4.3 of the Ansari et al. paper (at page 591) which describes the construction of the DNA target used for the *in vitro* transcription

experiment described in Ansari et al. See also Fig. 1 and the accompanying description in Arora et al.

The DNA target in both Ansari et al. and Arora et al. was fabricated with the appropriate palindromic recognition sequences for the polyamide DNA-binding domains. These palindromic recognition sequences were then purposefully placed in the proper orientation with respect to a downstream TATA box. Thus, in both Ansari et al. and Arora et al, an *in vitro* transcription assay was used wherein the artificial transcription factor was explicitly designed **to bind within an actual binding site** (and thus to initiate transcription via an interaction with the transcription machinery itself). See page 13068, right-hand column of Arora et al., and section 4.3, page 591 of Ansari et al.

Second, the ATFs of Ansari et al. combined with Arora et al. are explicitly designed to interact directly with "targets in the transcription machinery." See Ansari et al. at page 588, right-hand column, first full paragraph, and Fig. 1 of Arora et al. To accomplish that goal, both Ansari et al. and Arora et al. used a specific type of tether to project the activation domain away from the DNA (so that it can more easily interact with the transcriptional machinery). See page 589 of Ansari et al. and Fig. 1 of Arora et al. Thus, the combination of Ansari et al. with Arora et al. **does not** describe a construct that interacts with a gene-specific transcription factor or a regulatory factor. The combination of Ansari et al. with Arora et al. describes an artificial transcription factor itself. This is wholly different from the present invention. The present method does not use an artificial transcription factor, but employs a construct that interacts with a gene-specific transcription factor (or other regulatory factor). Thus, the present claims positively require two elements that are not described in the combination of Ansari et al. with Arora et al. First, the nucleic acid target of the present invention has bound to it an anchor moiety. However, unlike the combination of Ansari et al. with Arora et al., the anchor moiety in the present invention is bonded to the nucleic acid at a point "proximate to, but not within" the binding site for a regulatory factor. This is a positive limitation of all of the present claims. In contrast, the ATFs of Ansari et al. and Arora et al. must bind within the corresponding regulatory factor binding site on the DNA target to be transcribed.

Second, the present method uses a construct that interacts not with the transcription machinery (as in Ansari et al. and Arora et al.), but with a regulatory factor (such as a gene-

specific transcription factor). See Exhibits C and D, which illustrate schematically the method of Claim 1. Rather than being an ATF (as described in the combination of Ansari et al. with Arora et al.), the present invention uses a construct that includes an anchor that binds **outside of** the binding site for a transcription factor (or other regulatory factor). The anchor moiety of the present claims is depicted as "DBD" in Exhibits C and D. The anchor is connected to a linker, shown as a dashed line in Exhibits C and D. Lastly, a test compound, shown as a hook in Exhibits C an D is attached to the linker. In the present invention, the test compound interacts with DNA binding domain of a regulatory factor, such as a transcription factor.

This is different than the ATFs described in Ansari et al. and Arora et al. The present claims are not directed to ATFs, but to a method to evaluate test compounds for their ability to modulate the binding of regulatory factors (such as transcription factors) to their corresponding DNA binding sites. The composition recited in Claim 31 does not bind to the transcription binding site (as do the ATFs of Ansari et al. and Arora et al.), but binds proximate to it, so that the test compound can access and interact with the transcription factors (or other regulatory factors) that are capable of binding within the binding site. In short, the binding site remains open for regulatory factors to bind to it. The present method places a construct at a point proximate to the binding site (not within it) as a means to evaluate the test compound for its ability to interact with these regulatory factors.

Applicant therefore submits that the rejection of Claims 1, 11, 13, 20, 31, and 33 under §103(a) over Ansari et al. in view of Arora et al. is untenable. Withdrawal of the rejection is respectfully requested.

Rejection of Claims 1, 3, 6-9, 13, and 15-18 Under §103(a) over Ansari et al. (2001) in View of Ansari et al. (2002) *Curr. Opin. Chem. Biol.*, 6:765-772:

Ansari et al. (2001) has been addressed in several prior sections of this response. Those prior remarks are incorporated herein by reference. Briefly recapping, the Ansari et al. (2001) paper describes an artificial transcription factor. See section 1.2 of the Ansari et al. (2001) paper, starting at page 584, right-hand column. Thus, in Ansari et al. (2001), the authors constructed an artificial transcription factor that consisted of a polyamide DNA-binding domain (designed to bind to the sequence 5'-TGTTAT-3'), a flexible tether, and one of three different activation domains

based on VP16, a viral protein. A schematic diagram of this artificial transcription factor is shown in Fig. 1 of the Ansari et al. (2001) paper (at page 584) and in Exhibit B, attached hereto. As shown in Exhibit B, Ansari et al's artificial transcription factor very closely mimics a real transcription factor. Referring to Exhibit B, Ansari's artificial transcription factor consists of a DNA-binding domain ("DBD," blue triangle) linked to an activation domain ("AD," red hexagon), via a tether (black zig-zag line linking the DBD and the AD).

There are three critical distinctions between the artificial transcription factor taught by Ansari et al. (2001), and the method and composition of matter recited in the present claims. First, as noted earlier, the present claims are not directed to ATFs. Second, the artificial transcription factor described in Ansari et al. (2001) includes a polyamide DNA-binding domain that binds **within** the actual DNA recognition domain for the natural transcription factor. See Ansari et al., section 2.5, at page 590. See also section 4.3 of the Ansari et al. (2001) paper (at page 591) which describes the construction of the DNA target used for the *in vitro* transcription experiment described in Ansari et al. The DNA target was fabricated with the appropriate palindromic recognition sequences for the polyamide DNA-binding domains of Ansari's artificial transcription factor. These palindromic recognition sequences were then purposefully placed in the proper orientation with respect to a downstream TATA box. Thus, Ansari's *in vitro* transcription assay used a target DNA wherein the artificial transcription factor was explicitly designed **to bind within an actual binding site** (and thus to initiate transcription via an interaction with the transcription machinery itself). Third, the artificial transcription factor of Ansari et al. (2001) is explicitly designed to interact directly with "targets in the transcription machinery." See Ansari et al. (2001) at page 588, right-hand column, first full paragraph. To accomplish that goal, Ansari et al. used a longer tether (or incorporated an internal pyrrole residue into an otherwise short tether) to project the activation domain away from the DNA (so that it can more easily interact with the transcriptional machinery). See page 589 of Ansari. In other words, Ansari et al. (2001) **do not** describe a construct that interacts with a gene-specific transcription factor or a regulatory factor. Ansari et al. (2001) describe an artificial transcription factor itself.

Combining Ansari et al. (2001) with Ansari et al. (2002) does not add any further teaching to the 2001 paper because the two papers are largely cumulative. Most notably, however, see the section in Ansari et al. (2002) titled "DNA-binding domain," starting at page 766, right-hand

column. Note that the entire discussion in this section of the Ansari et al. (2002) paper is directed to DNA-binding domains "that target unique promoter sequences." Thus, combining the two Ansari et al. papers yields an ATF that includes a DNA-binding domain that targets a unique promoter sequence (*i.e.*, a transcription factor binding site).

This is distinctly different from the present invention. The present method does not use an ATF, but employs a construct that interacts with a transcription factor (or another regulatory factor). Thus, the present claims positively require two elements that are not described in the combination of the two Ansari et al. papers. First, the nucleic acid target of the present invention has bound to it an anchor moiety. However, **unlike the Ansari et al. papers**, the anchor moiety in the present invention is bonded to the nucleic acid at a point "**proximate to, but not within**" the binding site for a regulatory factor. This is a positive limitation of all of the present claims. In contrast, the artificial transcription factor of combined Ansari et al. papers must bind within the corresponding binding site on the DNA target to be transcribed. If it didn't bind within the corresponding binding site, the ATFs described by the combined Ansari et al. papers wouldn't work. Second, the present method uses a construct that interacts not with the transcription machinery (as in both of the Ansari et al. papers), but with a gene-specific regulatory factor (such as a transcription factor). See Exhibits C and D, which illustrate schematically the method of Claim 1. Rather than being an artificial transcription factor (as described in the Ansari et al. papers), the present invention uses a construct that includes an anchor that binds **outside of** the binding site for a transcription factor (or other regulatory factor). The anchor moiety of the present claims is depicted as "DBD" in Exhibits C and D. The anchor is connected to a linker, shown as a dashed line in Exhibits C and D. Lastly, a test compound, shown as a hook in Exhibits C an D is attached to the linker. In the present invention, the test compound interacts with DNA binding domain of a regulatory factor, such as a transcription factor.

This arrangement of elements is patentably distinct from the ATFs described in combination of the two Ansari et al. papers. The present claims are not directed to ATFs, but to a method to evaluate test compounds for their ability to modulate the binding of regulatory factors (such as transcription factors) to their corresponding DNA binding sites. In short, in the present invention, the binding site remains open for regulatory factors to bind to it. The present claims thus require that a construct be bound to the target DNA at a point proximate to the binding site,

but not within it.

Applicant therefore submits that the rejection of Claims 1, 3, 6-9, 13, and 15-18 under §103(a) over Ansari et al. (2001) in View of Ansari et al. (2002) is untenable. Withdrawal of the rejection is respectfully requested.

Rejection of Claims 22 and 29 Under §103(a) over Ansari et al. (2001), in View of Sadowski et al. and Arora et al.:

All of the Ansari et al (2001), Sadowski et al., and Arora et al. papers have been discussed in previous sections of this response. Those comments are incorporated herein by reference. Briefly recapping, the Ansari et al. (2001) paper describes an artificial transcription factor. See section 1.2 of the Ansari et al. (2001) paper, starting at page 584, right-hand column. Thus, in Ansari et al. (2001), the authors constructed an artificial transcription factor that consisted of a polyamide DNA-binding domain (designed to bind to the sequence 5'-TGTTAT-3'), a flexible tether, and one of three different activation domains based on VP16, a viral protein. A schematic diagram of this artificial transcription factor is shown in Fig. 1 of the Ansari et al. (2001) paper (at page 584) and in Exhibit B, attached hereto. As shown in Exhibit B, Ansari et al's artificial transcription factor very closely mimics a real transcription factor. Referring to Exhibit B, Ansari's artificial transcription factor consists of a DNA-binding domain ("DBD," blue triangle) linked to an activation domain ("AD," red hexagon), via a tether (black zig-zag line linking the DBD and the AD).

Sadowski et al. **do not** teach or suggest that the GAL4-VP16 is a transcription activator that can modulate binding of natural transcription factor, as alleged at the bottom of page 7 of the Office Action. Also, the binding sites for the GAL4 portion of Sadowski's construct were purposefully engineered into the CHO cells. Those binding sites are not present in the native CHO cells. See page 563, right hand column, first full paragraph of Sadowski et al.: "Reporter plasmids are distinguished by the presence (or absence) of insertions in the yeast sequence UAS_G that contains four GAL4 binding sites." Thus, Sadowski engineered into their construct the binding sites on the DNA target, and then positioned the binding sites at various locations relative to the gene to be transcribed. In effect, Sadowski simply engineered into their system a suitable binding site for their artificial transcription factor. But in every instance, the GAL4 portion of the

GAL4-VP16 construct binds **to that specific binding site** (which was inserted solely so that the GAL4-VP16 fusion protein would have place to bind).

Contrary to the assertion made by the Office, Sadowski et al. do not teach or suggest that their GAL4-VP16 "modulates" the binding of natural transcription factors to their corresponding natural binding sites. In fact, when the GAL4 binding site was omitted from the construct, no transcription resulted. See Sadowski et al. at page 566, left-hand column, first paragraph: "Activity was not detected in either cell line... when the UAS_0 was positioned at -1180 or +1850, and in no case did GAL4 activate."

Sadowski et al. also do not describe any type of linker between the GAL4 and the VP16 portions of their construct. Thus, looking at Ansari et al. in light of Sadowski et al. yields an artificial transcription factor as described by Ansari et al, with the parts slightly rearranged. Thus, the combination yields an artificial transcription factor consisting of Ansari's polyamide DNA-binding domain (or the GAL4 binding domain of Sadowski et al.), the polyether tether as taught by Ansari et al. (Sadowski's construct has no tether), and the VP-16 activation domain as described by Sadowski et al. The result is still an artificial transcription factor. The present claims, however, are not directed to an artificial transcription factor.

The Arora et al. patent likewise describes an artificial transcription factor in the same vein as Ansari et al. and Sadowski et al., except using a poly-L-proline linker. Thus, the full, three-way combination of Ansari et al., Sadowski et al., and Arora et al. teaches a modular, three-part ATF that is purposefully designed to bind within a transcription factor binding site.

As noted earlier, the present claims positively require two elements that are not described in the combined teachings of Ansari et al., Sadowski et al., and Arora et al. First, the nucleic acid target of the present invention has bound to it an anchor moiety. Unlike any of Ansari et al., Sadowski et al., and Arora et al., the anchor moiety in the present invention is bonded to the nucleic acid at a point "**proximate to, but not within**" the binding site for a regulatory factor. Clearly, this cannot be the case in the combination of Ansari et al., Sadowski et al., and Arora et al. because these three papers are all directed to ATFs that are designed to bind within a corresponding transcription factor binding site (so that the ATF will activate transcription of a desired downstream gene). All of the constructs described in Ansari et al., Sadowski et al., and Arora et al. interact with the transcription machinery itself, not other transcription factors.

Thus, the artificial transcription factor of Ansari et al., even when modified to include the GAL4 or the VP16 portions of Sadowski's construct, and the poly-L-proline tether of Arora et al. **must** bind within the binding site for the corresponding natural transcription factor binding site. Sadowski explicitly states that GAL4 binds within its corresponding regulatory binding site *in vivo*. And the Ansari et al. and Sadowski et al. papers are directed explicitly to artificial transcription factors per se, and not to constructs designed to interact with transcription factors.

In short, the present invention is not artificial transcription factor. The construct required by the present claims includes an anchor that binds **outside of the binding site for a transcription factor** (or other regulatory factor). The combination of Ansari et al., Sadowski et al., and Arora et al., in contrast, describes an artificial transcription factor that binds within the binding site for a natural transcription factor (GAL4- in the case of Sadowski et al.).

Claims 22 and 29 explicitly require that the construct used in the method binds at a point proximate to, **but not within**, the transcription factor binding site. None of Ansari et al (2001), Sadowski et al., and Arora et al., taken alone or in any combination, disclose or suggest this feature of the claimed invention because all three of these references describe artificial transcription factors per se. The present invention is not directed to ATFs, but to a method of evaluating test compounds for their ability to facilitate, recruit, or recruit the binding of transcription factors themselves to their corresponding binding sites on the DNA target.

Applicant therefore submits that the rejection of Claims 22 and 29 under §103(a) over Ansari et al. (2001), in view of Sadowski et al. and Arora et al. is untenable. Withdrawal of the rejection is respectfully requested.

Rejection of Claims 22 and 24-27 Under §103(a) over Ansari et al. (2001) in View of Sadowski et al. and Ansari et al. (2002):

All of the Ansari et al. (2001), Sadowski et al., and Ansari et al. (2002) papers have been discussed in previous sections of this response. Those comments are incorporated herein by reference. Briefly recapping, the Ansari et al. (2001) paper describes an artificial transcription factor. See section 1.2 of the Ansari et al. (2001) paper, starting at page 584, right-hand column. Thus, in Ansari et al. (2001), the authors constructed an artificial transcription factor that consisted of a polyamide DNA-binding domain (designed to bind to the sequence 5'-TGTTAT-

3'), a flexible tether, and one of three different activation domains based on VP16, a viral protein. A schematic diagram of this artificial transcription factor is shown in Fig. 1 of the Ansari et al. (2001) paper (at page 584) and in Exhibit B, attached hereto. As shown in Exhibit B, Ansari et al's artificial transcription factor very closely mimics a real transcription factor. Referring to Exhibit B, Ansari's artificial transcription factor consists of a DNA-binding domain ("DBD," blue triangle) linked to an activation domain ("AD," red hexagon), via a tether (black zig-zag line linking the DBD and the AD).

Sadowski et al. **do not** teach or suggest that the GAL4-VP16 is a transcription activator that can modulate binding of natural transcription factor, as alleged at the bottom of page 7 of the Office Action. Also, the binding sites for the GAL4 portion of Sadowski's construct were purposefully engineered into the CHO cells. Those binding sites are not present in the native CHO cells. See page 563, right hand column, first full paragraph of Sadowski et al.: "Reporter plasmids are distinguished by the presence (or absence) of insertions in the yeast sequence UAS_o that contains four GAL4 binding sites." Thus, Sadowski engineered into their construct the binding sites on the DNA target, and then positioned the binding sites at various locations relative to the gene to be transcribed. In effect, Sadowski simply engineered into their system a suitable binding site for their artificial transcription factor. But in every instance, the GAL4 portion of the GAL4-VP16 construct binds **to that specific binding site** (which was inserted solely so that the GAL4-VP16 fusion protein would have place to bind).

Contrary to the assertion made by the Office, Sadowski et al. do not teach or suggest that their GAL4-VP16 "modulates" the binding of natural transcription factors to their corresponding natural binding sites. In fact, when the GAL4 binding site was omitted from the construct, no transcription resulted. See Sadowski et al. at page 566, left-hand column, first paragraph: "Activity was not detected in either cell line... when the UAS_o was positioned at -1180 or +1850, and in no case did GAL4 activate."

Sadowski et al. also do not describe any type of linker between the GAL4 and the VP16 portions of their construct. Thus, looking at Ansari et al. in light of Sadowski et al. yields an artificial transcription factor as described by Ansari et al, with the parts slightly rearranged. Thus, the combination yields an artificial transcription factor consisting of Ansari's polyamide DNA-binding domain (or the GAL4 binding domain of Sadowski et al.), the polyether tether as taught

by Ansari et al. (Sadowski's construct has no tether), and the VP-16 activation domain as described by Sadowski et al. The result is still an artificial transcription factor. The present claims, however, are not directed to an artificial transcription factor.

The Ansari et al. (2002) paper does not add any further teaching to the Ansari et al (2001) and Sadowski et al papers because Ansari et al. (2002) is cumulative to Ansari et al. (2001). Most See, however, the section in Ansari et al. (2002) titled "DNA-binding domain," starting at page 766, right-hand column. The entire discussion in this section of the Ansari et al. (2002) paper is directed to DNA-binding domains "that target unique promoter sequences." Thus, combining the two Ansari et al. papers with Sadowski et al. yields an ATF that includes a DNA-binding domain that targets a unique promoter sequence (*i.e.*, a transcription factor binding site).

As noted earlier, the present claims positively require two elements that are not described in the combined teachings of Ansari et al. (2001), Sadowski et al., and Ansari et al. (2002). First, the nucleic acid target of the present invention has bound to it an anchor moiety. Unlike any of Ansari et al. (2001), Sadowski et al., and Ansari et al. (2002), the anchor moiety in the present invention is bonded to the nucleic acid at a point "**proximate to, but not within**" the binding site for a regulatory factor. Clearly, this cannot be the case in the combination of Ansari et al. (2001), Sadowski et al., and Ansari et al. (2002) because these three papers are all directed to ATFs that are designed to bind within a corresponding transcription factor binding site (so that the ATF will activate transcription of a desired downstream gene). All of the constructs described in Ansari et al. (2001), Sadowski et al., and Ansari et al. (2002) thus interact with the transcription machinery itself, and not with other transcription factors.

Thus, the artificial transcription factor of Ansari et al. (2001) when modified to include the GAL4 or the VP16 portions of Sadowski's construct, and DNA-binding domain of Ansari et al. (2002) **must** bind within the binding site for the corresponding natural transcription factor binding site. Sadowski explicitly states that GAL4 binds within its corresponding regulatory binding site *in vivo*. And all three of the Ansari et al. (2001), Sadowski et al., and Ansari et al. (2002) papers are directed explicitly to artificial transcription factors per se, and not to constructs designed to interact with transcription factors.

In short, the present invention is not directed to an artificial transcription factor. The construct required by the present claims includes an anchor that binds **outside of the binding site**

for a transcription factor (or other regulatory factor). The combination of Ansari et al. (2001), Sadowski et al., and Ansari et al. (2002), in contrast, describes an artificial transcription factor that binds within the binding site for a natural transcription factor.

Applicant therefore submits that the rejection of Claims 22 and 24-27 under §103(a) over Ansari et al. (2001) in view of Sadowski et al. and Ansari et al. (2002) is untenable. Withdrawal of the rejection is respectfully requested.

Rejection of Claims 1, 3, 8-9, 11, 13, 17-18, 20, 31, and 33 Under §103(a) over Felgner et al. (U.S. Patent No. 6,165,720) in view of Arora et al.:

The Felgner et al. patent describes an approach that is distinctly different from both the presently claimed invention, as well as the artificial transcription factors described in Arora et al. As noted at column 3, lines 24-45 of the Felgner et al. patent, Felgner et al. use a PNA-DNA hybrid vector, such as a plasmid. The PNA portion of the plasmid can be bound to a peptide or protein moiety, such as the activator domain of transcription factor. Note that Felgner et al. **do not** describe including in the construct a moiety that interacts with transcription factors themselves. As noted earlier, the activator domain of a transcription factor (natural or artificial) interacts directly with the transcription machinery (the RNA Pol II complex), **not** endogenous transcription factors themselves. This is explicitly taught in the Arora et al. reference. See Fig. 1 of Arora et al. and the accompanying description.

Applicant thus respectfully traverses this rejection because the combination of Felgner et al. with Arora et al. yields a PNA-DNA plasmid having attached thereto a linker as taught by Arora et al., at the end of which is attached a transcription activator domain. The construct lacks the required relationship between the location of the anchor moiety, and the location of the regulatory factor binding site. In short, Felgner's approach can only evaluate compounds for their ability to act as an **activator domain** that interacts directly with the transcription machinery, and not with gene-specific transcription factors themselves. The present claims positively require "determining whether binding of the regulatory factor to the binding site defined in the nucleic acid target is modulated by the presence of the test compound." See Claim 1. But Felgner's construct lacks both a regulatory factor binding site defined in the PNA-DNA construct, as well as any ability to modulate binding of a regulatory factor to the non-existent target site.

In Felgner's approach, a test compound that is a putative **transcription activation domain** is linked to the PNA portion of the plasmid (via Arora et al.'s linker). If the test compound functions as a transcription activator domain, it will interact directly with the RNA Pol II complex (as explicitly shown in Fig. 1 of Arora et al.). Felgner's test compound will not modulate binding of a regulatory factor to the binding site defined in the PNA-DNA vector because: (1) Felgner et al. do not define such a binding site in their plasmid; and (2) Felgner et al. only mention activation domains – compounds that react with the transcription machinery itself, not gene-specific regulatory factors, such as transcription factors.

Applicant therefore submits that the rejection of Claims 1, 3, 8-9, 11, 13, 17-18, 20, 31, and 33 under §103(a) over Felgner et al. in view of Arora et al. is untenable. Withdrawal of the rejection is respectfully requested.

CONCLUSION

In light of the above amendment and accompanying remarks, Applicant submits that the application is now in condition for allowance. Early notification of such action is earnestly solicited. If any questions arise, please contact the undersigned attorney. Telephone calls related to this application are welcomed and encouraged. The Commissioner is authorized to charge any fees or credit any overpayments relating to this application to deposit account number 18-2055.

Respectfully Submitted,

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